

NEUROTROPIC VIRUSES: CHARACTERISTICS OF RHABDOVIRUSES AND THEIR LABORATORY DIAGNOSIS

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Abstract: *Background: Rabies virus (RABV) is a classical neurotropic pathogen and the most lethal infectious agent known, belonging to the genus Lyssavirus within the family Rhabdoviridae. Although preventable, it continues to cause tens of thousands of human deaths annually, primarily in low- and middle-income countries, representing a persistent global public health challenge. Objective: To analyze the fundamental characteristics of neurotropic rhabdoviruses, with a focus on their structural features, replication cycle, neuropathogenesis, and the current laboratory diagnostic methods available for their detection. Methods: A narrative review of the literature was conducted, synthesizing information on the virology, pathogenesis, and diagnosis of rabies virus. Results: Rhabdoviruses are characterized by a unique bullet-shaped morphology and a single-stranded, negative-sense RNA genome encoding five structural proteins. Pathogenesis is defined by high neuroinvasiveness and neurotropism, with the virus traveling via peripheral nerves to the central nervous system. Laboratory diagnosis relies on post-mortem detection of viral antigen in brain tissue via the Direct Fluorescent Antibody Test (dFAT), considered the gold standard. Molecular methods, particularly real-time RT-PCR, have significantly improved diagnostic sensitivity and specificity. Conclusion: Rhabdoviruses are highly neurotropic pathogens with complex pathogenic mechanisms. A combination of traditional and modern molecular diagnostic techniques, primarily dFAT and RT-PCR, is essential for accurate and timely confirmation of infection.*

Keywords: *neurotropic virus, rhabdovirus, rabies virus, lyssavirus, laboratory diagnosis, RT-PCR, dFAT*

INTRODUCTION

Neurotropic viruses are defined by their unique ability to infect nerve tissue. The family Rhabdoviridae, belonging to the order Mononegavirales, encompasses a diverse group of viruses, with the rabies virus (RABV) of the genus Lyssavirus being the most significant human pathogen. Rabies is an acute, fatal zoonotic encephalitis that has been known since antiquity; the development of the first vaccine by Louis Pasteur in the 19th





century marked a major milestone in medical history. Despite this, RABV remains a formidable threat due to its near 100% case fatality rate once clinical symptoms appear and its ability to infect virtually any mammal. The virus is classified as a neurotropic pathogen due to its specific affinity for and ability to replicate within the nervous system, a feature that underpins the unique and severe pathogenesis of rabies. This article reviews the key characteristics of rhabdoviruses, with a specific focus on rabies virus, and describes the laboratory diagnostic approaches crucial for its identification and control.

Methods

A narrative review was conducted by searching electronic databases including PubMed, Scopus, Google Scholar, and ScienceDirect. The search period covered publications from 2000 to 2025. Keywords used included: "neurotropic virus", "rhabdovirus", "rabies virus", "lyssavirus", "laboratory diagnosis", "dFAT", and "RT-PCR". The review focused on articles detailing the virological characteristics, pathogenesis, and diagnostic methods for rabies virus. Key information was synthesized and structured into thematic sections covering viral morphology and genome, replication and pathogenesis, and laboratory diagnostics.

Results

General Characteristics and Taxonomy of Rhabdoviruses

Rhabdoviruses are enveloped viruses with a unique bullet-shaped or rod-like morphology, typically measuring approximately 180 nm in length and 75 nm in width. Their name is derived from the Greek word "rhabdos," meaning rod. The family Rhabdoviridae contains over 180 different viruses.

Within this family, three genera are recognized: Vesiculoviruses and Lyssaviruses, which can infect humans, and Ephemeroviruses, which are known only to infect animals. The genus Lyssavirus comprises at least 16 recognized viral species, including the prototype Rabies lyssavirus (RABV) and other bat-associated lyssaviruses distributed globally. RABV has an exceptionally wide host range, capable of infecting all mammals, due to its use of the evolutionarily conserved acetylcholine receptor for cellular entry.

Viral Structure and Genome Organization

The rabies virus particle (virion) consists of a single-stranded, negative-sense RNA genome enclosed within a helical nucleocapsid and surrounded by a host-derived lipid envelope. The genome is approximately 12,000 nucleotides in length and encodes five structural proteins. These proteins are: the nucleoprotein (N), which encapsulates the viral RNA; the phosphoprotein (P); the matrix protein (M); the glycoprotein (G), which forms spikes on the viral envelope and is responsible for receptor binding; and the large RNA-dependent RNA polymerase (L). The G protein is a key determinant of neurotropism and pathogenicity, mediating virus attachment to neural receptors and trans-synaptic spread.



Replication Cycle and Neuropathogenesis

Following a bite from a rabid animal, RABV replicates locally in muscle tissue at the entry site. It then enters the peripheral nervous system by binding to nicotinic acetylcholine receptors at the neuromuscular junction. The virus travels retrograde along the axonal microtubules of peripheral nerves to reach the central nervous system (CNS), a process defining its high neuroinvasiveness. In the CNS, RABV replicates rapidly within neurons, causing neuronal dysfunction, widespread inflammation (encephalomyelitis), and the characteristic clinical symptoms of rabies. From the CNS, the virus disseminates centrifugally along peripheral nerves to other tissues, including the salivary glands, which allows for viral shedding and transmission to new hosts. The ability of pathogenic "street" RABV strains to evade host immune responses is a critical factor in their lethality, in contrast to tissue culture-adapted "fixed" strains.

Clinical Manifestations

The incubation period in humans is highly variable, ranging from days to over a year, but is typically 20–90 days. Initial, non-specific symptoms include malaise, fever, and headache. As the disease progresses, two main clinical forms can emerge: furious rabies, characterized by hyperactivity, hydrophobia (fear of water), aerophobia, and agitation; and paralytic (or dumb) rabies, which is marked by progressive muscle weakness and paralysis. Regardless of the form, the disease invariably progresses to coma and death, typically within days of symptom onset, unless intensive life support is provided.

Laboratory Diagnosis

Prompt and accurate laboratory confirmation of rabies is critical for patient management and public health surveillance. The diagnostic methods are summarized in Table 1.

Method Principle Specimen Type Application

Direct Fluorescent Antibody Test (dFAT) Detection of rabies virus antigen in nervous tissue using fluorescently-labeled anti-rabies antibodies Brain tissue (post-mortem) Gold standard for post-mortem diagnosis

Reverse Transcription PCR (RT-PCR) Amplification of rabies virus RNA (e.g., N or G gene) for detection Saliva, CSF, urine, brain tissue (post-mortem) Ante-mortem diagnosis; high sensitivity and specificity

Rapid Detection Test (RDT) Immunochromatographic assay for antigen detection Brain tissue Rapid screening tool; good agreement with FAT

Histopathology Microscopic examination for Negri bodies (eosinophilic inclusion bodies) and lymphoplasmacytic meningoencephalitis Brain tissue (post-mortem) Confirmatory; rule out other causes



Virus Isolation Cell culture inoculation to amplify the virus Brain tissue, saliva
Definitive diagnosis (rarely used as primary method)

Post-mortem Diagnosis

The gold standard for rabies diagnosis is the Direct Fluorescent Antibody Test (dFAT) performed on brain tissue. This test provides rapid and reliable results with excellent sensitivity (99.72–100%) and specificity (99.99–100%) when compared to other methods. It detects rabies virus antigen in the cytoplasm of infected neurons. Reverse Transcription PCR (RT-PCR), including real-time quantitative PCR (qPCR) assays like the LN34 assay, is increasingly used as a confirmatory tool and has shown excellent performance, resolving inconclusive cases from dFAT. Rapid detection tests (RDTs), using lateral flow technology, have demonstrated high agreement with dFAT ($\kappa = 1$) and are valuable for field use and in resource-limited settings. Histopathological examination revealing Negri bodies and characteristic meningoencephalitis can support the diagnosis.

Ante-mortem Diagnosis


Diagnosis before death is more challenging but can be achieved using a combination of tests. RT-PCR on multiple samples, such as saliva, cerebrospinal fluid (CSF), and urine, is the most sensitive ante-mortem approach. Virus isolation from saliva or CSF is also possible but is less practical. Detection of neutralizing antibodies in serum or CSF is another criterion, but serology may only become positive late in the disease or after vaccination.

Discussion

Rabies virus exemplifies the archetypal neurotropic pathogen. Its ability to circumvent the immune system and migrate along neural pathways to the CNS, where it causes severe and irreversible damage, underlies its extraordinary lethality. The pathogenesis is complex and multigenic, with the viral glycoprotein playing a central role in neural cell entry and trans-synaptic spread, while other genetic elements contribute to its high neuroinvasiveness. Despite the development of highly effective pre- and post-exposure prophylaxes, rabies remains a neglected zoonotic disease, claiming an estimated 59,000 lives annually, with the majority of cases occurring in regions where access to these measures is limited.

From a diagnostic perspective, significant advancements have been made. The dFAT remains an irreplaceable gold standard for post-mortem confirmation due to its speed and accuracy. However, the widespread adoption of molecular diagnostics, particularly real-time RT-PCR, has revolutionized the field. The high sensitivity and specificity of modern PCR assays, such as the LN34 pan-lyssavirus assay, allow for rapid and reliable diagnosis, even in cases where the dFAT yields inconclusive results. The development of rapid, easy-to-use point-of-care tests has also improved surveillance capabilities in low-resource settings.





However, challenges persist. Ante-mortem diagnosis remains difficult, and no single test is 100% sensitive. Access to diagnostic facilities is often lacking in the areas most heavily burdened by rabies. Furthermore, the existence of other lyssaviruses with divergent genetic sequences necessitates the use of pan-lyssavirus diagnostic assays to avoid false negatives. Future directions should focus on developing more affordable, field-deployable molecular tests and integrating rabies diagnosis into broader surveillance networks for emerging zoonotic diseases.

Conclusion


Rhabdoviruses, particularly rabies virus, are highly neurotropic pathogens that cause one of the most lethal infectious diseases known to humans. Their unique morphology, genetic organization, and sophisticated neural transmission mechanisms define their pathogenesis. The laboratory diagnosis of rabies relies on a hierarchical approach, moving from rapid antigen detection via dFAT and RDTs to confirmatory molecular testing by RT-PCR. While traditional methods remain foundational, the integration of advanced molecular tools is critical for improving diagnostic accuracy, conducting surveillance, and ultimately supporting global efforts to eliminate human rabies.

Continued investment in laboratory infrastructure, training, and research into novel diagnostic platforms is essential to mitigate the impact of this ancient and enduring disease.

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